Remarks

Reconsideration of this Application is respectfully requested.

Claims 17 and 34 are sought to be cancelled without prejudice to or disclaimer of the subject matter therein and claims 3, 5 and 33 are sought to be amended. Upon entry of the foregoing amendment, claims 1-5 and 33 are currently under consideration in the application, with claims 1, 2, 3 and 5 being the independent claims.

Support for the amendments to the claims can be found throughout the specification and in the claims as originally filed. *See, e.g.*, Specification pages 11-15, 18. These changes are believed to introduce no new matter, and their entry is respectfully requested.

Based on the above amendments and the following remarks, Applicants respectfully request that the Examiner reconsider all outstanding objections and rejections and that they be withdrawn.

Election/Restrictions

The Examiner acknowledged Applicants' election with traverse of Group I (claims 1-5, 17, and 33-34, full length SEQ ID NO:2). *See* Paper No. 15, page 2. Since it was the Examiner's view that Applicants' arguments were not persuasive, the Examiner deemed the requirement proper and therefore made it final. *See id.* The Examiner also indicated that claims 1-5, 17, and 33-34 as drawn to generic fragments of SEQ ID NO:2 were under consideration. *See id.*at 4.

Objections

The Examiner objected to claim 33 "because it is drawn to the same composition as claim 17." Paper No. 15, page 4.

In response to the Examiner's objection, Applicants have cancelled claim 17 thereby rendering the objection moot.

The Examiner objected to claims 33 and 34 "because they depend on non-elected claim 18." Paper No. 15, page 4. Applicants have amended claim 33 to no longer depend from claim 18, and Applicants have cancelled claim 34, thereby rendering the objection moot.

Based on these amendments, the Examiner is respectfully requested to reconsider and withdraw all outstanding objections.

Rejections under 35 U.S.C. § 112, Second Paragraph

The Examiner rejected claims 3, 5, and 34 under 35 U.S.C. § 112, second paragraph, as allegedly being indefinite for failing to particularly point out and distinctly claim the subject matter which Applicants regard as the invention because of the use of language "derived from". *See* Paper No. 15, page 4. Applicants have cancelled claim 34 and have amended claims 3 and 5 to no longer recite "derived from", thus this rejection has been rendered moot. Accordingly, the Examiner is respectfully requested to withdraw the rejection.

Rejection under 35 U.S.C. § 101

The Examiner rejected claims 1-5 and 33-34 under 35 U.S.C. § 101 stating that "the claimed invention is not supported by either a specific asserted utility or a well established utility." Paper No. 15, page 5. Claim 34 has been cancelled rendering the rejection moot as it applies to claim 34. Further, claim 3 has been amended to more particularly point out and distinctly describe Applicants' invention. Applicants traverse the rejection as it applies to claims 1–5 and 33.

The Examiner stated:

> The specification discloses isolation of a polynucleotide of SEQ ID NO:1, which is assumed to encode SEQ ID NO:2 (p.8, lines 16-19). The specification further discloses that SEQ ID NO:1 is overexpressed in kidney cancer as compared to normal kidney (p.7 and figure 2). No disclosure is found in the specification concerning detection of the expression or overexpression of the putative encoded protein SEQ ID NO:2 in any cancer tissue. The specification also discloses potential MHC-binding peptide fragments from SEQ ID NO:2 (P.29-30). However no disclosure is found in the specification concerning the actual detection of the presentation of these fragments by CTL's in any cancer patients.

Paper No. 15, page 5.

Applicants note that under 35 U.S.C. § 101 the "specific asserted utility or a well established utility" requirement is met by only one credible assertion of a specific utility. *See, e.g., Raytheon v. Roper*, 220 U.S.P.Q. 592, 598 (Fed. Cir. 1983), *cert. denied*, 469 U.S. 835 (1984) ("When a properly claimed invention meets at least one stated objective, utility under 35 U.S.C. § 101 is clearly shown.").

Further, the manner of using an invention disclosed in a specification must be accepted by the PTO "unless there is reason to doubt the objective truth of the statements contained therein." *In re Marzocchi*, 58 C.C.P.A. 1069, 439 F.2d 220, 223, 169 U.S.P.Q. 367, 369 (C.C.P.A. 1971); *see also Utility Examination Guidelines*, 66 Fed. Reg. 1092, 1098-99 (Jan. 5, 2001) (" *Utility Guidelines*"). Instances in which an assertion of specific utility is not credible are rare. *See* MPEP § 2107 (7th ed. Rev. 1, Feb. 2000). Indeed, the Federal Circuit affirmed the standard for making a utility rejection that was set forth in *In re Brana*, 51 F.3d 1560, 34 U.S.P.Q.2d 1436 (Fed. Cir. 1995):

> The PTO cannot make this type of rejection . . . unless it has reason to doubt the objective truth of the statements contained in the written description. *See Brana*, 51 F.3d at 1566, 34 USPQ2d at 1441.

In re Cortright, 49 U.S.P.Q.2d 1464, 1466 (Fed. Cir. 1999). The PTO's own guidelines provide:

> Any rejection based on lack of utility should include a detailed explanation why the claimed invention has no specific and substantial credible utility. Whenever possible, the examiner should provide documentary evidence . . . (e.g., scientific or technical journals, excerpts from treatises or books, or U.S. or foreign patents) to support the factual basis for the prima facie showing of no specific and substantial credible utility. If documentary evidence is not available, the examiner should specifically explain the scientific basis for his or her factual conclusions.

Utility Guidelines, 66 Fed. Reg. at 1098. Further, the Federal Circuit has articulated the standard for utility: "The threshold of utility is not high: An invention is 'useful' under section 101 if it is capable of providing some identifiable benefit." *Brenner v. Manson*, 383 U.S. 519, 534 (1996); *Brooktree Corp. v. Advanced Micro Devices*, Inc., 977 F.2d 1555, 1571 (Fed. Cir. 1992) ("To violate § 101 the claimed device must be totally incapable of achieving a useful result"); *Fuller v. Berger*, 120 F. 274, 275 (7th Cir. 1903) (test for utility is whether invention "is capable of serving any beneficial end"). *Juicy Whip, Inc. v. Orange Bang Inc.*, 185 F.3d 1364, 1366, 51 U.S.P.Q.2d 1700, 1702 (Fed. Cir. 1999).

The Examiner has not made the required showing that even one, much less all, of the disclosed utilities for SEQ ID NO:2, or immunogenic fragments thereof, would be unbelievable in light of the teachings of the specification -- under either the standard set forth in *Juicy Whip* or the PTO's guidelines. By the Examiner's own admission, Applicants have disclosed "making antibodies specific for SEQ ID NO:2 or fragments thereof, induction of an immune response, such as induction of CTL's or antibodies, and treating or preventing cancer." Paper No. 15 page 5. Any one of these uses are sufficient to satisfy the "specific utility" requirement.

However, the Examiner alleges that "no actual treatment of any cancer using the claimed SEQ ID NO:2 or fragments thereof is found in the specification." Paper No. 15, pages 5-6. In support of the rejection the Examiner proffers unrelated examples of the regulation of gene

expression by the regulation of mRNA translation, and stating that because in certain instances genes are not expressed, "one of ordinary skill in the art would not be able to predict if SEQ ID NO:1 is translated into a polypeptide expression product, or even if translated, whether it is over expressed" Paper No. 15, pages 7. Such a prediction, or lack thereof, is not relevant to utility unless the Examiner can provide evidence that the invention is "incapable" of being used as claimed.

Applicants have shown that the clone R11, the sequence of which is shown in SEQ ID NO:1, is expressed in various tumors with little or no expression in normal tissues. *See*, Specification, page 7, lines 3-9. One of ordinary skill in the art would in fact predict that SEQ ID NO:1 encodes the polypeptide SEQ ID NO:2, unless there was a specific teaching to the contrary. *See* Specification, page 8, lines 16-19. The Examiner has provided no evidence to suggest that there are any reasons to doubt that SEQ ID NO:1, in particular, does not in fact translate into the polypeptide SEQ ID NO:2, or fragments thereof as predicted.

Further, the specification is replete with disclosure regarding the selection of immunogenic R11 peptides by, *inter alia*, MHC-binding and CTL induction, and use of such selected peptides for treatment of R-11-ORF-1- and R-11-ORF-2-positive tumors, particularly, carcinoma of the breast, kidney cells, and pancreas (by administration, *inter alia*, of antibodies generated from the R11 peptide or TAA vaccine). *See*, Specification pages 11-15, 18.

Further, the specification teaches use of the R11 polypeptides as diagnostic reagents. *See*, Specification page 16. In particular, Applicants point to Example 4, wherein R11- specific primers showed expression by qualitative PCR in human pancreatic tumors, and various human tumor cell lines, all contrary to the Examiner's assertion of no such teaching.

Therefore, Applicants have certainly provided some identifiable benefit under *Juicy Whip*, and their utility is specific and substantial under the PTO's guidelines. The Examiner has not

provided any evidence or sound scientific reasoning to establish that an artisan would reasonably doubt all of the asserted utilities described above. Thus, Applicants respectfully request withdrawal of this rejection.

Rejection Under 35 U.S.C. § 112, first paragraph - Written Description

The Examiner rejected claims 3 and 34 under 35 U.S.C. § 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the art that the inventors, at the time the application was filed, had possession of the claimed invention. *See* Paper No.15, page 8. As stated above, claim 34 has been cancelled. Applicants respectfully traverse this rejection as it may apply to claim 3.

The Examiner states that "[c]laims 3, 34 encompass [sic] polypeptide of any length, and any structure, provided said polypeptides share with SEQ ID NO:2 a common fragment, which could as little as a few amino acids." Paper No. 15, page 9.

Further, the Examiner stated:

> The instant specification fails to provide sufficient descriptive information, such as definitive structural or functional features of the claimed genus of polypeptides. There is no description of the conserved regions which are critical to the structure and function of the genus claimed. There is no description, however, of the sites at which variability may be tolerated and there is no information regarding the relation of structure to function. Structural features that could distinguish the compounds in the genus from other excluded are missing form the disclosure. Furthermore, the prior art does not provide compensatory structural or correlative teachings sufficient to enable one of skill to isolate and identify the polypeptides encompassed and no identifying characteristics or property of the instant invention polypeptides is provided such that one of skill would be able to predictably identify the encompassed molecules as being identical to those instantly claimed.

Paper No. 15, pages 9-10.

The test for the written description requirement is whether one skilled in the art could reasonably conclude that the inventor has possession of the claimed invention in the specification as filed. *Vas-Cath Inc. v. Mahurkar*, 935 F.2d 1555, 1563, 19 USPQ2d 1111, 1116 (Fed. Cir. 1991); M.P.E.P. § 2163.02. The Examiner bears the initial burden of presenting a *prima facie* case of unpatentability. This burden is discharged if the Examiner can present evidence or reasons why one skilled in the art would not reasonably conclude that Applicants possessed the subject matter as of the priority date of the present application. *In re Wertheim*, 541 F.2d 257, 262, 191 USPQ2d 90, 96 (C.C.P.A. 1976); M.P.E.P. § 2163.04.

Claim 3 has been amended to more clearly recite both structural and functional properties. Claims 3 recites "An immunogenic protein fragment of SEQ ID NO:2, wherein said fragment is presented by an MHC-molecule and induces or augments a cellullar immune response." Applicants note that claim 3 is directed to a fragment of the amino acid sequence of SEQ ID NO:2 and is defined by a specific functional utility. Thus, both structural and functional characteristics are defined.

The specification defines the "immunogenic fragments" of claim 3 as those which are presented by an MHC-molecule and induce or augment a cellular immune response. Such peptides have allele specific requirements for each MHC-I allele product in order for the peptide to bind MHC molecules and thereby trigger a cellular immune response. Specification, pages 11-12. Tables 1 and 2 provide ample examples of such peptide fragments.

Thus, the specification supports the functional component of claim 3, which, in conjunction with the structural recitation of SEQ ID NO:2, provides sufficient written description of the claimed invention. Claim 3 has the additional structural requirement of MHC binding in order for antigen presentation to occur.

Further, amended claim 3 clearly meets the Written Description Guidelines. *See, Synopsis of Application of Written Description Guidelines* ("*The Guidelines*").

Example 13 in *The Guidelines* sets forth a hypothetical claim 2 reciting "[a]n isolated variant" of a protein comprising SEQ ID NO:3. *The Guidelines*, p. 50. According to Example 13, the hypothetical specification describes SEQ ID NO:3 by complete structure, and defines "variant" as being a protein with one or more "substitutions, deletions, insertions and/or additions" in SEQ ID NO:3. *Id.* No individual variants are described. *Id.* *The Guidelines* state that "[t]he specification and claim do not place any limit on the number of amino acid substitutions, deletions, insertions and/or additions that may be made to SEQ ID NO:3," and the claimed genus therefore "is highly variant because a significant number of structural differences between genus members is permitted." *Id.*, p. 51. *The Guidelines* conclude that "SEQ ID NO:3 alone is insufficient to describe the genus" and the claim should be rejected as not being adequately described. *Id.*, p. 51-2.

In contrast to claim 2 in Example 13, the claimed genus is not highly variant, since all of the claimed immunogenic protein fragments are presented by an MHC-molecule and induce or augment a cellular immune response. In addition, Applicants have provided an assay for determining allele-specific requirements of each MHC product with regard to a peptide that binds to an MHC-molecule and is thereby presented by the MHC-molecule, and applicants have taught an assay for determining activity of these peptides in inducing or augmenting an cellular immune response. *See, e.g.*, Specification, pages 11-13. Thus, the present situation is distinguishable from the situation for claim 2 in Example 13.

Example 14 of *The Guidelines* sets forth a hypothetical claim reciting polypeptide variants "at least 95% identical to SEQ ID NO:3" and having catalytic activity. *The Guidelines*, p. 53. The hypothetical specification in Example 14 discloses SEQ ID NO:3, and "contemplates but does not

exemplify variants of the protein" that contain substitutions, deletions, insertions and/or additions. *Id.* Further, *The Guidelines* state that "the genus of proteins that must be variants of SEQ ID NO:3 does not have substantial variation since all of the variants must possess the specified catalytic activity and must have at least 95% identity to the reference sequence." *Id.*, p. 54. *The Guidelines* conclude that "[t]he single species disclosed is representative of the genus" and "[o]ne of ordinary skill in the art would conclude that applicant was in possession of the necessary common attributes possessed by the members of the genus." *Id.*, p. 54-55.

Like Example 14, the present specification describes, and the claims recite, variants having a limited number of differences and having a common activity. Therefore, Applicants submit that the claimed genus is *not* highly variant and SEQ ID NO:2 *is representative* of the genus. Like Example 14, therefore, the present claims are adequately described by the specification.

It is believed that all of the Examiner's concerns with regard to 35 U.S.C. § 112, first paragraph, for alleged lack of written description have been fully addressed. Accordingly, Applicants respectfully request that the rejection of the claim 3 under 35 U.S.C. § 112, first paragraph, for alleged lack of written description be reconsidered and withdrawn.

Rejection Under 35 U.S.C. § 112, first paragraph - Enablement/Scope

The Examiner rejected claims 4-5, 17 and 33-34 under 35 U.S.C. § 112, first paragraph, as allegedly containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to make and/or use the invention. Claims 17 and 34 have been cancelled, thus the rejection as it applies to these claims has been rendered moot. Applicants respectfully traverse this rejection as it applies to the remaining claims.

The Examiner stated:

> The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims. . . .One cannot extrapolate the teaching of the specification to the claims because it is well known that the art of anticancer drug discovery for cancer therapy is highly unpredictable . . .Because of the unpredictability of the art, in the absence of experimental evidence, no one skilled in the art would accept the assertion that the claimed polypeptide or fragments thereof are effective in treating tumors.

Paper No. 15, pages 12-16.

In order to satisfy the enablement requirement of 35 U.S.C. § 112, first paragraph, the claimed invention must be enabled so that any person skilled in the art can make and use the invention without undue experimentation. *See In re Wands*, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988). The information necessary to practice the invention can originate, not only from Applicants' specification, but also from the knowledge generally possessed by those in the art. *See Genentech, Inc. v. Novo Nordisk*, 108 F.3d 1361, 1366, 42 USPQ2d 1001, 1005 (Fed. Cir. 1997); *In re Howarth*, 654 F.2d 103, 105-6, 210 USPQ 689, 692 (CCPA 1981); *see also In re Brebner*, 455 F.2d 1402, 173 USPQ 169 (CCPA 1972). As discussed in detail below, a person of ordinary skill in the art would be able to practice the full scope of the invention encompassed by the claims without undue experimentation.

The Examiner has relied on unpredictability as a basis for alleging that the claims are non-enabled. Applicants note however, that "unpredictability [in the art may] . . . be enough to create reasonable doubt as to the accuracy of a particular broad statement put forward as enabling support for a claim, [t]his will be . . . the case where the statement is, on its face, *contrary* to generally accepted scientific principles." *In re Marzocchi*, 439 F.2d 220, 223 (C.C.P.A. 1971) (emphasis added).

There are no statements in the specification that were contrary to generally accepted scientific principles at the time the application was filed. In addition, the fact that experimentation may be complex does not necessarily make it undue, if the art typically engages in such experimentation. *See In re Certain Limited-Charge Cell Culture Microcarriers*, 221 USPQ 1165, 1174 (Int'l Trade Comm'n 1983), *aff'd. sub nom., Massachusetts Institute of Technology v. A.B. Fortia*, 227 USPQ 428 (Fed. Cir. 1985). As the Examiner stated, researchers "sift through potential anticancer agents" and "strategies to overcome defense mechanisms of neoplastic cells have been developed and tested in a number of patients;" thus, experimentation to make and use the claimed invention is acceptable, and in fact, is common place in the art of cancer therapy.

Further, mere unpredictability of the result of the experiment is not a consideration. Indeed, in *In re Angstadt*, the Court of Custom and Patent Appeals has specifically cautioned that the unpredictability of the result of an experiment is not a basis to conclude that the amount of experimentation is undue:

> [If to fulfill the requirements of 112, first paragraph, an applicant's] disclosure must provide guidance which will enable one skilled in the art to determine, with reasonable certainty before performing the reaction whether the claimed product will be obtained, . . . then all "experimentation" is "undue" since the term "experimentation" implies that the success of the particular activity is uncertain. Such a proposition is contrary to the basic policy of the Patent Act.

537 F.2d at 503, 190 USPQ at 219 (emphasis in the original). Thus, Examiner's statement that "no one skilled in the art would accept the assertion that the claimed polypeptide and fragments thereof are effective in treating cancers" goes beyond the 35 U.S.C. § 112, first paragraph enablement requirement.

Contrary to the Examiner's assertions, Applicants have enabled immunogenic fragments of SEQ ID NO:2, the claimed TAA or fragments thereof that induce a cellular or humoral immune

response, and pharmaceutical compositions comprising the TAA antigen of SEQ ID NO:2 or fragments thereof. In particular, Applicants have cited specific mechanisms for generating peptides and identifying which are immunogenic according to the claimed invention.

> The present invention relates to immunogenic polypeptide and fragments derived from R11-ORF-1 or R11-ORF-2. The latter are hereinafter referred to as R11 peptides. A first group are the R11 peptides which trigger a humoral immune response (induction of antibodies). Such peptides are selected portions of R11-ORF-1 or R11-ORF-2 (at least 6 amino acids) which can be determined by so-called prediction algorithms such as for example the surface probability plot (Emini et al., 1985 J. Virol. 55: 836-839), the hydrophobicity plot (kyte and Doolittle, 1982 J. Mol. Biol. 157: 105-132 and the antigenic index (Jameson and Wolf, 1988 Comput. Appl. Biosci. 4: 181-186).

Specification, pages 9-10. Further, the specification states that the production of antibodies following administration of peptides identified according to the methods cited above, can be measured by common immunological assays, such as ELISA. *Id.*

The R11 peptides within the scope of the invention, identified as those which are presented by MHC-molecules and induce or augment a cellular immune response, are also enabled by the specification. The Specification teaches how such peptides can be selected, *i.e.* by the allele specific requirements for binding MHC-I molecules, and to assay such binding peptides for CTL induction. *See, e.g.*, Specification, pages 10-13, and Example 7, listing potential MHC-binding peptides in the regions coding for two reading frames of R11.

With this guidance, one of ordinary skill in the art is given sufficient guidance on how to make and used the claimed invention with a level of experimentation that is expected in the art, rather than undue. Further, with the use of the disclosed algorithm, the unpredictability of the results of such experimentation is minimized. *See* Specification, page 30 (describing the Parker et al.

algorithm and listing candidate fragments that can be expected to bind corresponding HLA molecules and therefore constitute immunogenic CTL-epitopes).

Accordingly, the Examiner is respectfully requested to reconsider and withdraw the rejection of claims 4-5 and 33 under 35 U.S.C. § 112, first paragraph.

Rejection under 35 U.S.C. § 102(b)

The Examiner also rejected claim 3 under 35 U.S.C. § 102(b) as allegedly being anticipated by U.S. Patent No. 6,184,356 (hereinafter "the '356 patent"). *See* Paper No. 15, page 16. Specifically, the Examiner asserted that "US 6184356 teaches a sequence SEQ ID NO:32, which is 100% similar to a fragment of SEQ ID NO:2, from amino acid 48-56. . .Given the peptide sequence taught by US 6184356, one of ordinary skill in the art would immediately envision the claimed polypeptide fragment." Paper No. 15, pages 16-17. Applicants traverse this rejection.

Claim 3 has been amended to recite "[a]n immunogenic protein fragment of SEQ ID NO:2, wherein said fragment is presented by an MHC-molecule and induces or augments a cellular immune response."

Anticipation of a claim under 35 U.S.C § 102(b) can be found only if the prior art reference discloses each and every element as set forth in the claim. *See Glaxo Inc. v. Novopharm Ltd.*, 34 USPQ2d 1565, 1567 (Fed. Cir. 1995), *cert denied,* 116 S. Ct. 516 (1995).

SEQ ID NO:32 of the '356 patent is merely an intertetrameric linker sequence consisting of 9 prolines contained within a protein. While this fragment is identical to amino acids 48-56 of SEQ ID NO:2, nothing in the '356 patent teaches that this fragment or the protein the fragment is contained within, is presented by an MHC-molecule and produces a cellular immune response as required in claim 3 (to the contrary the '356 patent is directed to pseudotetrameric hemoglobin-like proteins). Thus, each and every element of claim 3 is not found in the prior art reference identified

by the Examiner, as such a rejection 35 U.S.C. § 102(b) is inappropriate. Accordingly, Applicants respectfully request that the Examiner reconsider this rejection and that it be withdrawn.

Conclusion

All of the stated grounds of objection and rejection have been properly traversed, accommodated, or rendered moot. Applicants therefore respectfully request that the Examiner reconsider all presently outstanding objections and rejections and that they be withdrawn. Applicants believe that a full and complete reply has been made to the outstanding Office Action and, as such, the present application is in condition for allowance. If the Examiner believes, for any reason, that personal communication will expedite prosecution of this application, the Examiner is invited to telephone the undersigned at the number provided.

Prompt and favorable consideration of this Amendment and Reply is respectfully requested.

Respectfully submitted,

STERNE, KESSLER, GOLDSTEIN & FOX P.L.L.C.

Eric K. Steffe
Attorney for Applicants
Registration No. 36,688

Date 6/18/03

1100 New York Avenue, N.W.
Suite 600
Washington, D.C. 20005-3934
(202) 371-2600

Version with Markings to Show Changes Made

Claims 17 and 34 have been cancelled.

Claims 3, 5 and 33 have been amended as follows:

3. An immunogenic protein fragment [derived from the TAA of claim 1] of SEQ ID NO:2, wherein said fragment is presented by an MHC-molecule and induces or augments a cellular immune response.

5. An immunogenic protein fragment [of claim 3] of SEQ ID NO:2, wherein [the protein] said fragment induces or augments a humoral immune response

33. A pharmaceutical composition comprising the tumor-associated antigen of claim 1[or claim 18]; and a pharmaceutically acceptable carrier.